

APPLICATION  
FOR  
UNITED STATES LETTERS PATENT

TITLE: METHOD OF USING SECRETIN AND COMPOSITIONS  
MADE THEREFROM FOR THE TREATMENT OF AUTISM  
AND OTHER NEUROLOGICAL, BEHAVIORAL AND  
IMMUNOLOGICAL DISORDERS

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METHOD OF USING SECRETIN AND COMPOSITIONS MADE THEREFROM  
FOR THE TREATMENT OF AUTISM AND OTHER NEUROLOGICAL, BEHAVIORAL  
AND IMMUNOLOGICAL DISORDERS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 60/088,575 filed June 9, 1998, fully incorporated herein by reference, and is a continuation-in-part of United States patent Application No. 09/080,631 filed May 18, 1998 and entitled Method For Assisting in Differential Diagnosis And Treatment Of Autistic Syndromes.

FIELD OF THE INVENTION

The present invention relates to methods and compositions for the treatment of neurological, behavioral and/or immunological disorders and more particularly, to a new medical use for the natural or synthetic hormone secretin in the treatment of autism and other neurological, behavioral and/or immunological disorders.

BACKGROUND OF THE INVENTION

Autism is a disabling neurological disorder that affects thousands of Americans and encompasses a number of subtypes, with various putative causes and few documented ameliorative treatments. The disorders of the autistic spectrum may be present at birth, or may have later onset, for example, at ages two or three. There are no clear cut biological markers for autism. Diagnosis of the disorder is made by considering the degree to

1 which the child matches the behavioral syndrome, which is  
2 characterized by poor communicative abilities, peculiarities in  
3 social and cognitive capacities, and maladaptive behavioral  
4 patterns.

5 A number of different treatments for autism have been  
6 developed. Many of the treatments, however, address the symptoms  
7 of the disease, rather than the causes. For example, therapies  
8 ranging from psychoanalysis to psychopharmacology have been  
9 employed in the treatment of autism. Although some clinical  
10 symptoms may be lessened by these treatments, modest improvement,  
11 at best, has been demonstrated in a minor fraction of the cases.

12 Only a small percentage of autistic persons become able to  
13 function as self-sufficient adults.

14 Although much controversy exists about the causes and  
15 treatments of autism, a few established biomedical findings have  
16 been made. Many individuals with autism experience intestinal  
17 difficulties, often including the inability to digest gluten and  
18 casein. Abnormalities have also been found in the metabolism of  
19 the neurotransmitter serotonin and in various parameters of immune  
20 system functions, for example, elevated Measles, Mumps and Rubella.  
21 (MMR) titers. Prior to the discovery of the present invention,  
22 however, no useful links had been made between these biomedical  
23 findings, nor had any successful treatments been derived  
24 therefrom, as disclosed in various articles incorporated herein by  
25 reference.<sup>1</sup>

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<sup>1</sup> Priven, J. (1997). The biological basis of autism. Current Opinion in Neurobiology, 7, 708-712.

Rapin, L. & Katzman, R. (1998). Neurobiology of autism. Ann Neurology, 43, 7-14.

1 Similar to autistic spectrum disorder, many other behavioral,  
2 neurological and immunological disorders have been equally  
3 difficult to understand and to effectively treat. Such disorders  
4 include depression, obsessive-compulsive disorder, Alzheimer's,  
5 allergies, anorexia, schizophrenia, as well as other neurological  
6 conditions resulting from improper modulation of neurotransmitter  
7 levels or improper modulation of immune system functions, as well  
8 as behavioral disorders such as ADD (Attention Deficit Disorder)  
9 and ADHD (Attention Deficit Hyperactivity Disorder), for example.  
10 Accordingly, a need exists for a method and composition for the  
11 treatment of autism and other behavioral, neurological and/or  
12 immunological disorders.

13 The hormone secretin is a polypeptide hormone secreted by the  
14 mucosa of the duodenum and upper jejunum when acid chyme enters  
15 the intestine. The hormone secretin stimulates the pancreatic  
16 acinar cells to release bicarbonate and water, which are excreted  
17 into the duodenum and change the pH in the gut from acid to  
18 alkaline, thereby facilitating the action of digestive enzymes.  
19 Secretin is always used and indeed is intended only to be used in  
20 diagnostic tests given to patients with gastrointestinal disorders.  
21 to stimulate the release of pancreatic juices for testing  
22 purposes.

23 Prior to the discovery of the present invention, however  
24 secretin has never before been linked to autistic spectrum  
25 disorders, either as a possible cause or treatment, nor has it  
26 been used in the treatment of other neurological and/or

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Wing, L. (1997). The autistic spectrum. The Lancet, 350 (dec. 13), 1761-1765.

immunological disorders, as herein proposed.

### SUMMARY OF THE INVENTION

The present invention features a method for the treatment of neurological, immunological and other disorders in a patient.

The method comprises the step of stimulating the secretion of pancreatic juices in the patient. In one embodiment, stimulating the secretion of pancreatic juices comprises the step of administering to the patient an effective amount of natural or synthetic secretin. The preferred method of the present invention is for the treatment of autistic spectrum disorder.

According to one method of administering secretin, the secretin is administered by infusion and the effective amount is generally 2 clinical units (CU) per kilogram (kg) of body weight given intravenously within 1 minute. In another method, the secretin is administered transdermally by applying a transdermal carrier substance, such as dimethyl sulfoxide (DMSO) to the skin, applying crystalline secretin in an effective amount onto the carrier substance, and rubbing the composition into the skin.

One example of an effective amount of secretin administered transdermally includes about 15 CU of crystalline secretin.

Other methods of administering secretin include, but are not limited to, administering secretin transdermally with a gel, lotion or patch; administering secretin with a suppository; administering secretin orally, as tablet, capsule or lozenge; administering secretin by inhalation (e.g., as an aerosol) either through the mouth or the nose; and administering secretin using acoustic waves to permeate the skin. The present invention

1 also contemplates other physiologically acceptable carriers or  
2 excipients for carrying an effective amount of secretin into the  
3 patient's body.

4 In another embodiment, the method for stimulating the  
5 secretion of pancreatic juices comprises the step of causing the  
6 body to secrete secretin in an effective amount to at least  
7 ameliorate and preferably treat autism and other neurological  
8 and/or immunological disorders. This method includes, for  
9 example, stimulating or otherwise causing the duodenum and upper  
10 jejunum to secrete the hormone secretin for one or more of the  
11 purposes described herein.

12 The present invention also features compositions for use  
13 according to the above methods. In one embodiment, a  
14 pharmaceutical composition, according to the present invention  
15 includes an effective amount of secretin together with a suitable  
16 volume of sodium chloride for dissolving the secretin and  
17 carrying the secretin into the body by infusion. In another  
18 embodiment, a composition according to the present invention  
19 includes an effective amount of secretin and a transdermal  
20 carrier substance, such as DMSO for carrying the secretin into  
21 the body transdermally. Other compositions include an effective  
22 amount of secretin together with physiologically acceptable  
23 carriers or excipients for carrying the secretin into the  
24 patient's body. The present invention contemplates the use of  
25 both natural and synthetically produced secretin.

#### 26 27 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

28 The present invention will be better understood from the

1 following examples which are given by way of illustration and not  
2 by way of limitation. The patient, the same in both examples, is  
3 a boy with symptoms of autism. Although only two examples of  
4 treatment are presented on the same patient, the present invention  
5 has been tried on a number of children in accordance with the  
6 method of the first example with similar satisfactory results.

7 The patient in the present examples developed normally until  
8 about fourteen months of age, with the exception of  
9 gastrointestinal problems (i.e., chronic diarrhea and  
10 constipation) which began at about six months. At about thirteen  
11 months, when whole milk was introduced into his diet, the patient  
12 began having reoccurring ear infections. At about fourteen  
13 months, the patient appeared to lose the ability to process  
14 language, first receptively (at about 14 months) then expressively  
15 (at about 16 months). The patient also experienced episodes of  
16 "shivers" that appeared to be intermittent seizures.

17 After consulting with numerous neurologists, pediatricians,  
18 child development specialists, audiologists, endocrinologists,  
19 allergists, and other medical professionals, no consistent  
20 diagnosis had been reached. Although not clinically diagnosed  
21 with autism, the patient exhibits a number of behavioral symptoms  
22 of autism and pervasive developmental disorder (PDD) in general.  
23 The term autism is used herein for reference purposes only, and  
24 this invention is intended to apply to any number of pervasive  
25 developmental disorders as well as neurological and immunological  
26 disorders.

27 Prior to receiving the treatment with secretin, a single  
28 photon emission computed tomography (SPECT) scan of the brain

1 revealed a decreased perfusion in the right hemisphere and left  
2 temporal lobe, with the most severe decrease in the right parietal  
3 occipital region. Also, steady state auditory evoked responses  
4 recorded in response to rapid amplitude and frequency modulations  
5 of a 1 kHz tone were abnormal, suggesting disturbances of neural  
6 mechanisms responsible for frequency and amplitude modulation  
7 analysis. Further, the patient's secretin cells prior to  
8 receiving treatment, measured at a level of 9, are far below the  
9 normal limit in the range of 20-70.

#### 10 EXAMPLE 1

11 When the patient was three years old, the secretin was  
12 administered by way of an infusion as part of an upper  
13 gastrointestinal endoscopy. The secretin was used in this  
14 diagnostic procedure at the request of the patient's parents, one  
15 of which is an inventor of the present invention. The secretin  
16 used in this procedure is known as Secretin-Ferring available from  
17 Ferring Laboratories, Inc., Suffern, New York (See Appendix A).  
18 The secretin was dissolved in a 7.5 solution of sodium chloride  
19 and administered in a dosage of 2 clinical units (CU) per kilogram  
20 (kg) body weight by intravenous injection over one minute. (I.E.  
21 30 IU IV for approximately 15 kilograms of body weight.)

22 Immediately after the administration of the secretin, the  
23 diagnostic testing revealed that the patient's pancreas responded,  
24 quite surprisingly, with an unusually large amount of pancreatic  
25 juice being released (approximately 10 ml/min compared to a usual  
26 rate of 1-2 ml/min). The diagnostic tests performed on the  
27 patient during this procedure also indicated gastric inflammation.

28 Within days after the administration of secretin, the patient's



1 chronic abnormal bowel movements became normal, although no  
 2 changes had been made in the patient's diet. Within weeks after  
 3 the treatment, the patient was able to make normal eye contact,  
 4 language appeared for the first time in two years, and other  
 5 behavioral and developmental problems improved remarkably. The  
 6 following Table I summarizes the improvements observed in the  
 7 patient within 3 weeks after the infusion of secretin.

8 Table I

Symptoms Before Secretin Infusion	Progress within 3 Weeks After the Secretin Infusion
Two words	100's of words - will repeat some approximation of any work requested.
No sentences	Short sentences - such as; "I love you", "I want juice", "Good night mommy", "Thank you, daddy".
No flash cards	40 - 50 flash cards.
No focus on requested tasks	Will sit and watch carefully. Will perform most tasks after watching once or twice. For instance, will sort by color or category. Will construct more complicated puzzles. Will respond appropriately to questions.
Diapers only	Completely potty trained.
Watch Videos	Now, gets "involved" interactively with his videos. He will imitate the hand motions, sing the songs or dance to the music.
Consistent sleeping problems. Although these were much worse when he was 18-24 months, prior to the procedure he was still up numerous times each night.	Has slept through almost every night entirely.
Infrequent (1-2 times/week) "spinning" episodes.	No spinning episodes.
Abnormal bowel movements	Normal bowel movements.
Excessive water consumption approximately 50 cups per day.	Excessive water consumption - no change approximately 50 cups per day.
Limited Diet Preferences (French Toast, bananas, French Fries, pancakes, crackers, cookies, raisins, chocolate, chicken nuggets.)	No Change
No apparent connections made between language and objects.	Many connections made between new language learned and objects. Recites names he has learned on flash cards when he sees the same

	on computer game or video.
No response to request for gestures.	Responds to all kinds of things such as, "blow a kiss", "Wave bye bye", "Say bye bye", etc. Will often now spontaneously say these things himself.
No interest in drawing	Wants to draw constantly. Will draw complete face and name the parts as he draws.
Did not imitate commands.	Will imitate almost any multi-step command.
Minimal eye contact	Eye contact 75% of the time.

Biomedical changes were also measured in the patient. A SPECT scan of the patient indicated that the perfusion of the right posterior parietal and right temporal lobes was improved. Blood tests taken after the treatment also indicated a rise in serotonin levels, and the patient's rubella titers dropped from 5.8 to 2.3.

Although the behavioral improvements continued, the rate of the patient's progress appeared to decrease at about 5 weeks. At the request of the patient's parents, a second infusion of secretin was performed about 9 months after the first infusion, and a third infusion of secretin was performed about three months after the second infusion. The second and third infusions of secretin achieved the same results in the patient.

## EXAMPLE 2

At the time of this treatment, the patient was about 4 years old. Secretin was administered transdermally using pharmaceutical grade dimethyl sulfoxide (DMSO) (generally 99.9% pure) available from Clinic Service Co., Box 2512, Hemet CA 92543. The secretin (Secretin-Ferring) was administered daily in a dosage of about 75 CU over a five day period (i.e., about 15 CU daily). For each treatment, about 4 drops of DMSO were placed onto the skin of the

1 patient, about 15 CU of the crystalline secretin was placed onto ,  
2 the DMSO, and the composition was rubbed into the skin.

3 The administration of secretin transdermally on a daily basis  
4 in this way has resulted in even more dramatic and significant  
5 improvements in the patient. Within a period of about 6 months,  
6 the patient has progressed to spontaneous and conversational  
7 language. When the daily dose of secretin is stopped, the  
8 autistic behavioral symptoms return.

9 It is important to note that similar results have been seen  
10 in numerous other autistic children using an intravenous  
11 administration of secretin in accordance with the teachings of the  
12 present invention, in order to validate the findings of the  
13 present invention.

14 Although the present invention is not limited by theory, it  
15 is believed that some autistic spectrum disorders are caused by a  
16 secretin deficiency resulting in a dysfunction of the pancreas.  
17 One function of the hormone secretin is to stimulate the pancreas  
18 to release bicarbonate and water, which change the pH in the gut  
19 from acid to alkaline, thereby facilitating the action of  
20 digestive enzymes. The gastrointestinal disorders, such as an  
21 inability to digest gluten and casein, in autistic patients is  
22 possibly caused by this failure of the pancreas to release  
23 enzymes.

24 One possibility is that abnormal opioid peptides in the gut  
25 create problems in the brain. These abnormal opioid peptides have  
26 been found to diminish on a casein free and gluten free diet.  
27 According to one study, autistic children that responded to this  
28 diet were given an infusion of secretin and the peptides were

1 measured before and after the secretin infusion. After the  
2 secretin infusion, which stimulates the pancreas to release  
3 bicarbonate, the peptides disappeared.

4 The gastric inflammation observed in the patient in the above  
5 EXAMPLE 1 suggests that the improper pH resulting from this  
6 dysfunction of the pancreas may be a cause of the digestive  
7 problems and malabsorption of essential minerals and nutrients  
8 found in many individuals with autism. The unusual secretion by  
9 the pancreas in response to the secretin, as observed in EXAMPLE  
10 1, further suggests that this dysfunction of the pancreas is  
11 caused by a secretin deficiency.

12 In addition to this effect on the digestive function,  
13 secretin also appears to improve the abnormal brain activity in  
14 individuals having symptoms of autism. The increased blood flow  
15 in the brain detected during a SPECT scan after administering  
16 secretin in EXAMPLE 1 supports this theory. While causing  
17 pancreatic secretions, secretin also stimulates the production of  
18 cholecystokinin (CCK). Deficiencies in CCK have been linked to  
19 other neurological disorders, such as schizophrenia, and CCK  
20 production has been found to be related to levels of the  
21 neurotransmitter serotonin. Thus, secretin may be indirectly  
22 related to the body's natural production of serotonin. The  
23 increase in serotonin levels in the blood after the procedure in  
24 EXAMPLE 1 supports this relationship between secretin and  
25 serotonin.

26 Without proper modulation of neurotransmitter levels (i.e.,  
27 serotonin) in the brain, the brain will not function properly.  
28 The inability to modulate neurotransmitter levels has been found

1 to be related to other neurological conditions as well as autism.  
2 Thus, a secretin deficiency may cause an imbalance or improper  
3 modulation of neurotransmitter levels that results in autistic  
4 spectrum disorder or other neurological disorders. Administering  
5 secretin to patients with these disorders will modulate the  
6 neurotransmitter levels and correct the behavioral symptoms, such  
7 as the inability to process language and other maladaptive  
8 behavioral patterns. The secretin may also correct abnormalities  
9 in immune system functions, as indicated by the reduction of  
10 measles, mumps and rubella antibodies in the patient after the  
11 secretin administration in EXAMPLE 1. Secretin has also been  
12 found to stimulate dopamine production through its precursor,  
13 tyrosine hydroxylase. Dopamine levels have been implicated in a  
14 variety of mental and behavioral disorders such as Parkinson's and  
15 Alzheimer's disease.

16 A secretin deficiency can therefore account for the  
17 gastrointestinal disorders as well as the behavioral symptoms  
18 found in many individuals with autistic spectrum disorder.

19 The therapeutic possibilities of the use of secretin appear  
20 to have been overlooked in the medical literature. For example,  
21 Guyton and Hall, in their widely used Textbook of Medical  
22 Physiology (9th edition, 1995-1997) mention briefly in passing  
23 that secretin can increase cellular utilization of insulin.  
24 Recent research suggests that insulin is required for normal brain  
25 functioning. (See also Science vol. 280 April 24, 1998, p. 517-  
26 518). Furthermore, immunological disorders related to abnormally  
27 high levels of measles, mumps, and rubella (MMR) titers may also

1 be treatable with secretin. Additionally, secretin is believed to  
2 stimulate antibodies to cows milk protein (and perhaps other  
3 proteins). Autism and other PDD's may be connected to protein  
4 intolerance and secretin may increase the body's tolerance to such  
5 protein(s). Secretin may also have histamine blocking  
6 capabilities.

7 Although the above examples use Secretin-Ferring, the present  
8 invention contemplates other forms of natural or synthetic  
9 secretin. The present invention also contemplates using other  
10 types of transdermal carrier substances in addition to DMSO.

11 Further, the present invention contemplates other alternative ways  
12 of administering secretin including, but not limited to,  
13 administering secretin transdermally with a gel, lotion or patch;  
14 administering secretin with a suppository; administering  
15 secretin orally, as tablet, capsule or lozenge; administering  
16 secretin by inhalation (e.g., as an aerosol) either through the  
17 mouth or the nose. Such alternative methods of administering  
18 secretin are less invasive, do not have to be carried out by a  
19 doctor at a medical facility, and are less expensive. In  
20 addition, the level or dose of administration of secretin can be  
21 varied from those examples stated herein including, for example,  
22 intravenous administration over a period of time of several  
23 hours instead of several minutes and/or a smaller, maintenance or  
24 daily dose administered intramuscularly, transdermally or by  
25 other methods as disclosed herein or their equivalent.

26 A further alternative method of transdermally administering  
27 secretin includes the use of acoustic waves to permeate the skin.  
28 For example, acoustic waves generated using ultrasound or a

1 shockwave from a pulsed laser have been found to make the skin  
2 temporarily permeable. A few minutes of low-frequency ultrasound  
3 (sound greater in frequency than 20 kilohertz) creates tiny  
4 cavities through which the secretin (alone or combined with  
5 another transdermal carrier substance) can be diffused.

6 Accordingly, the method of treating autism by  
7 administering secretin and/or causing the body to naturally  
8 secrete required amounts of secretin corrects the secretin  
9 deficiency, improving the digestive functions in autistic patients  
10 previously experiencing intestinal difficulties and improving  
11 communication, cognition, and socialization capabilities of  
12 autistic patients. Since other neurological disorders, such as  
13 depression, obsessive-compulsive disorder, Alzheimer's, allergies,  
14 anorexia, bulimia, schizophrenia, also involve abnormal modulation  
15 of neurotransmitter levels, these disorders may also be treatable  
16 with secretin. Further, other disorders related to serotonin and  
17 dopamine may also be treatable with secretin.

18 Modifications and substitutions by one of ordinary skill in  
19 the art are considered to be within the scope of the present  
20 invention which is not to be limited except by the claims which  
21 follow.

22 What is claimed is: